Adrenergics (SNS)

Introduction

We introduced the adrenergic system in General Pharmacology #8: *Intro to Autonomics* when we went over the cardiovascular system and the eye. There we said what the adrenergic system did, and introduced the adrenergic receptors α_1, α_2, β_1, and β_2, but didn't discuss how those receptors work. In this lesson, we will start with a bit of a review—what the receptors are and their effects on the organs where they are found. We then transition into a very atypical approach to pharmacology, Dr. Williams' version of vasopressors utilizing the adrenergic receptors to guide it. We then spend the rest of the lesson drilling down to the level of the synapse, the release and metabolism of norepinephrine at the synaptic cleft, and the unique endocrine adrenergic system of the adrenal medulla and circulating epinephrine, and focus most of our attention on exploring the mechanisms and intracellular messengers of adrenergic receptors.

Review: Receptors and Their Effects

There are four adrenergic receptors—α_1, α_2, β_1, and β_2.

β_1 receptors are found on the **1 heart**. There is only one heart, and β_1 receptors are found there. β_1 receptors are not found anywhere else. β_1 receptors are found on cardiac pacemakers of the AV node—stimulation leads to an increased heart rate. β_1 receptors are found on ventricular myocytes—stimulation leads to the heart's beating harder, an increased contractility.

β_2 receptors are found on the **2 lungs**. There are two lungs, and β_2 receptors are found there. Stimulation of β_2 in the lung leads to bronchodilation. β_2 receptors are also found in skeletal muscle. Stimulation of β_2 receptors in the vasculature of skeletal muscles leads to vasodilation, and a resultant decrease in blood pressure. β_2 receptors are not innervated, and therefore are not stimulated by norepinephrine. They are stimulated only by circulating epinephrine.

α_1 is present on **blood vessels**. Stimulation of α_1 receptors results in smooth muscle contraction of the blood vessel. This leads to vasoconstriction and a resultant increase in blood pressure. α_1 receptors are also present in the **eye**, and when activated stimulate the radial muscle which dilates the pupil.

α_2 is present on presynaptic neurons, where norepinephrine release from the presynaptic neuron stimulates α_2 on the presynaptic neuron, turning off norepinephrine release from that same presynaptic neuron. α_2 acts to self-regulate norepinephrine release. This is inhibitory autocrine signaling.

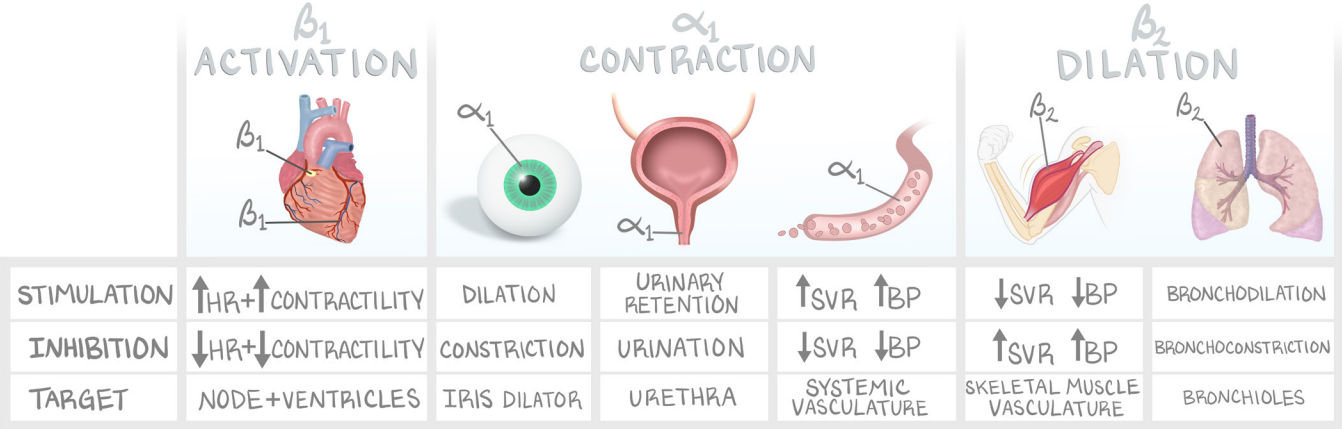
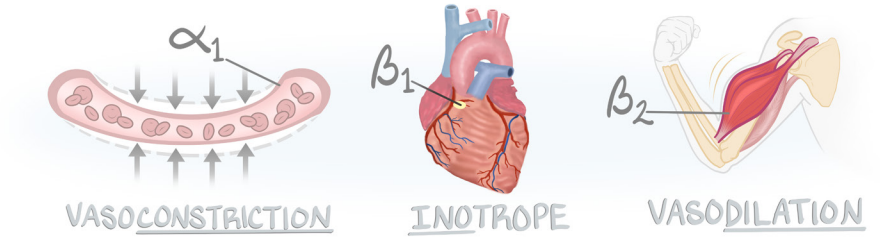


Figure 10.1: Adrenergic Receptor Effects on Organs
Visual organizer for the effects that adrenergic receptors have on various visceral organs. α_2 has no "organ effect" and is discussed in the section on mechanisms, below.

Vasopressors—A Bridge between Mechanism of Action and Clinical Medicine

If you look to most pharmacology textbooks regarding adrenergics, what you see is a table, usually with drug name on the leftmost column, then columns titled by the adrenergic receptor. This creates an awful grid which is near impossible to memorize, consisting of pluses and minuses, each plus representing how much a given vasopressor activates a given adrenergic receptor. WE ADVOCATE STRONGLY FOR NEVER LOOKING AT THAT CHART AND NEVER MEMORIZING WHAT IT SAYS.

Instead, we give you Dr. Williams' approach to vasopressors, used in real practice and also on board examinations. Vasopressors are infused medications that are used to alter hemodynamics, generally to restore blood pressure. Dr. Williams breaks it down as shown in Figure 10.2, below. All of these are **agonists** of adrenergic receptors. The most important part of this breakdown for your basic science understanding is to realize that stimulation of an adrenergic can lead to vasoconstriction or vasodilation.



α_1 VASOCONSTRICTORS	β_1 α_1 INO - CONSTRICTORS	β_1 β_2 INO - DILATORS
PHENYLEPHRINE VASOPRESSIN *EPINEPHRINE*	NOREPINEPHRINE DOPAMINE	MILRINONE DOBUTAMINE

Figure 10.2: Dr. Williams' Approach to Vasopressors
A simplified approach to vasopressors for clinical practice. This method allows the division of vasopressors into three categories, translation of the category titles to which adrenergic receptor they activate, and also linking of specific drugs to specific diagnosis. Although grossly oversimplified compared to other pharmacology textbooks, the real-world application and ease of memorization makes this a far superior method. Epinephrine, although used as a vasoconstrictor in practice, is the exception, as it activates all but α_2 adrenergic receptors. Epinephrine's overall effect is depicted in Figure 10.1.

A **"-constrictor"** will constrict the blood vessels, and therefore will increase blood pressure. Blood pressure goes up by improving systemic vascular resistance. Constrictors activate **α_1**.

An **"ino"** is short for inotrope (that is, INO-tropic and not IONO-tropic, as in the receptor that opens an ion channel). Inotropes make the heart work harder. Since there is only one heart, **β_1 receptors** are on the heart. Therefore, inotropes stimulate β_1 receptors. That results in an increased heart rate and stronger contractility.

A **"-dilator"** will dilate blood vessels, and therefore will decrease blood pressure. The only adrenergic receptors that reduce blood pressure when activated are found in the vasculature of skeletal muscle. These β_2 receptors are stimulated only by epinephrine and receive no innervation by norepinephrine. We can infuse β_2 agonists.

Now look at Figure 10.2 again. The words can be replaced by the receptors they stimulate. You may know nothing of cardiogenic shock, sepsis, or anaphylaxis, but already you can get a feel for the name of the drug and its Dr. Williams Class, and link it to the adrenergic receptors they stimulate.

Epinephrine is the exception. Epinephrine falls into the vasoconstrictor category because of HOW it is used, not its mechanism. Anaphylaxis is treated with epinephrine, and it is primarily for the vasoconstrictor effects (opposed to the bronchodilator effects demonstrated in movies and TV). When used as the third agent in septic shock, it is the α_1 vasoconstriction we are after. But the movies aren't totally wrong. Epinephrine, the endogenous compound from the adrenal medulla and the drug that is injected to reverse anaphylaxis, stimulates α_1, β_1, and β_2. α_1 gives vasoconstriction, β_1 increases heart rate, and β_2 dilates bronchioles. So what we recommend is to learn "Dr. Williams' vasopressors," and then memorize epinephrine's mechanism, since "Dr. Williams' vasopressors" was originally used for internal medicine interns in the ICU.

Pharmacology Mechanisms

Norepinephrine is released from nerve terminals of postganglionic neurons and activates adrenergic receptors on effector organs—only organs innervated by autonomic neurons receive a norepinephrine signal. α_1, α_2, and β_1 receptors are stimulated by norepinephrine. Any stimulation by norepinephrine **requires autonomic innervation**, which means that transplanted organs are not modulated by norepinephrine. Indirect agonists (such as amphetamine and norepinephrine reuptake inhibitors) require norepinephrine release and cannot affect denervated tissues. α_2 receptor activation turns off norepinephrine release, and its discussion is reserved for the next section, "The Neurotransmitter Cycle."

Epinephrine is released from the adrenal medulla in response to preganglionic release of acetylcholine. Epinephrine is a hormone that circulates through the bloodstream. Because epinephrine circulates through the blood, there is no α_2 receptor at a presynaptic neuron, and therefore epinephrine does not simulate α_2 receptors. Also because epinephrine circulates through the blood, it can activate receptors that are not directly innervated by postganglionic neurons; therefore it can activate β_2 receptors. There are no indirect agonists for epinephrine. Epinephrine activates α_1, β_1, and β_2 receptors.

α_1 stimulation causes the contraction of smooth muscle. Some smooth muscle, as in the peripheral vasculature, is circumferential. Contraction of circumferential muscle around a blood vessel causes the blood vessel to constrict, increasing resistance, thereby increasing blood pressure. Contraction of smooth muscle of the radial muscle of the eye causes the muscle to pull the iris open, dilating the eye. In both cases, smooth muscle contracts. From General Pharmacology #7: *Receptors and Second Messengers* we learned that contraction of smooth muscle occurs from the influx of calcium, and contraction of smooth muscle is usually through the second messenger system **G_q-IP_3-DAG-Ca**. α_1 is stimulated by epinephrine and norepinephrine.

β_1 stimulation causes excitable cells activation. "Activation" is via intracellular phosphorylation, activation of the **G_s-cAMP-PKA** intracellular second messenger system. β_1 receptors are found on the 1 heart, and are present on both ventricular myocytes and AV nodal cells. In nodal cells, "activation" of excitable cells causes conduction velocity to increase, increasing the heart rate. In ventricular myocytes, "activation" of excitable cells causes increased ventricular contractility. The combination is a heart that beats faster (nodal cells) and harder (ventricular myocytes). Be cautious: cardiac myocytes are like skeletal muscle—they contract harder when there is more calcium. Calcium and muscular contraction of SMOOTH MUSCLE was α_1-G_q. But calcium and muscular contraction of CARDIAC MUSCLE is β_1-G_s. Learn that **β receptors** use the **G_s-cAMP-PKA** intracellular second messenger system. β_1 is stimulated by both norepinephrine and epinephrine.

β_2 Stimulation is best left to memorization. β Receptors use G_s-cAMP-PKA. β_2 follows that rule. But **β_2**-receptor activation leads to **dilation**. α_1-G_q leading to contraction makes intuitive sense because calcium influxes. β_1-G_s activating cardiac tissue is easy to accept. But there is no logical deduction that activation of PKA and phosphorylation of intracellular targets leads to dilation. And yet, the message from the last paragraph rings true: β-receptors use the G_s-cAMP-PKA intracellular second messenger system. And β_2 receptors are found in bronchioles and skeletal muscle vasculature. In the lungs, β_2 stimulation leads to **bronchodilation**. In the skeletal muscle vasculature, β_2 stimulation leads to **vasodilation** (and a drop in blood pressure). β_2 receptors are stimulated only by circulating epinephrine.

α_2 Receptors are present only on postganglionic nerve terminals. Only norepinephrine is released from postganglionic nerves, so only norepinephrine stimulates α_2 receptors. When α_2 receptors are stimulated, norepinephrine release is inhibited. The release of norepinephrine from presynaptic neurons activates presynaptic neuro **α_2 receptors**, which **turn off the release of norepinephrine**.

	NOREPI?	EPI?	ORGAN AND EFFECT	SECOND MESSENGER SYSTEM
α_1	Yes	Yes	Vasculature—contraction = ↑ SVR = ↑ BP Eyes—contraction radial muscle = pupillary dilation	G_q-IP_3-DAG-Ca
β_1	Yes	Yes	Heart, nodal cells = ↑ HR Heart, myocytes = ↑ contractility	G_s-cAMP-PKA
β_2	No	Yes	Lungs—dilation = bronchodilation Sk muscle vasculature—dilation = ↓ SVR = ↓ BP	G_s-cAMP-PKA
α_2	Yes	No	Presynaptic norepinephrine release inhibition	N/A

Table 10.1: Adrenergic Receptor Mechanisms
Summary table of the adrenergic receptors, which adrenergic chemical signal activates each receptor, the receptor effect on the target organ, and the receptor intracellular second messenger.

The Neurotransmitter Cycle of Norepinephrine

This section is going to review the steps in norepinephrine synthesis, compare it to the synaptic cleft in regard to acetylcholine, and summarize the activity of adrenergic receptors. This section is NOT going to review all of the drugs that are involved with the norepinephrine synapse. Norepinephrine is used in more than just the effector synapse between postganglionic sympathetic fibers and their effector organ cells. Norepinephrine is a neurotransmitter throughout the central nervous system. The location of the synapse, and between which types of neurons, will determine its effect. Likewise, norepinephrine metabolism can be impacted by drugs—the more specific the drug, the fewer the side effects; the less specific the drug, the more unintended locations of norepinephrine metabolism will be affected and the more side effects there will be. **Do not learn receptor subtypes**. That level of detail is far beyond medical school. Instead, simply identify how many disease states and how many medication classes there are that can impact "norepinephrine" outside the autonomics.

We identify and discuss medication classes in reference to norepinephrine metabolism, but don't go into specifics. Instead, we discuss the medications in reference to the disease they treat. We talk about reuptake inhibitors and MAO inhibiters in lessons on depression and anxiety in Psych, COMT-inhibitors in a neurology lesson on Parkinson's, and α_2 blockers in hypertension. The goal here is to introduce the neurotransmitter cycle and reference which adrenergic receptor does what and how, with a sprinkling of what's to come in future lessons outside of The Cell.

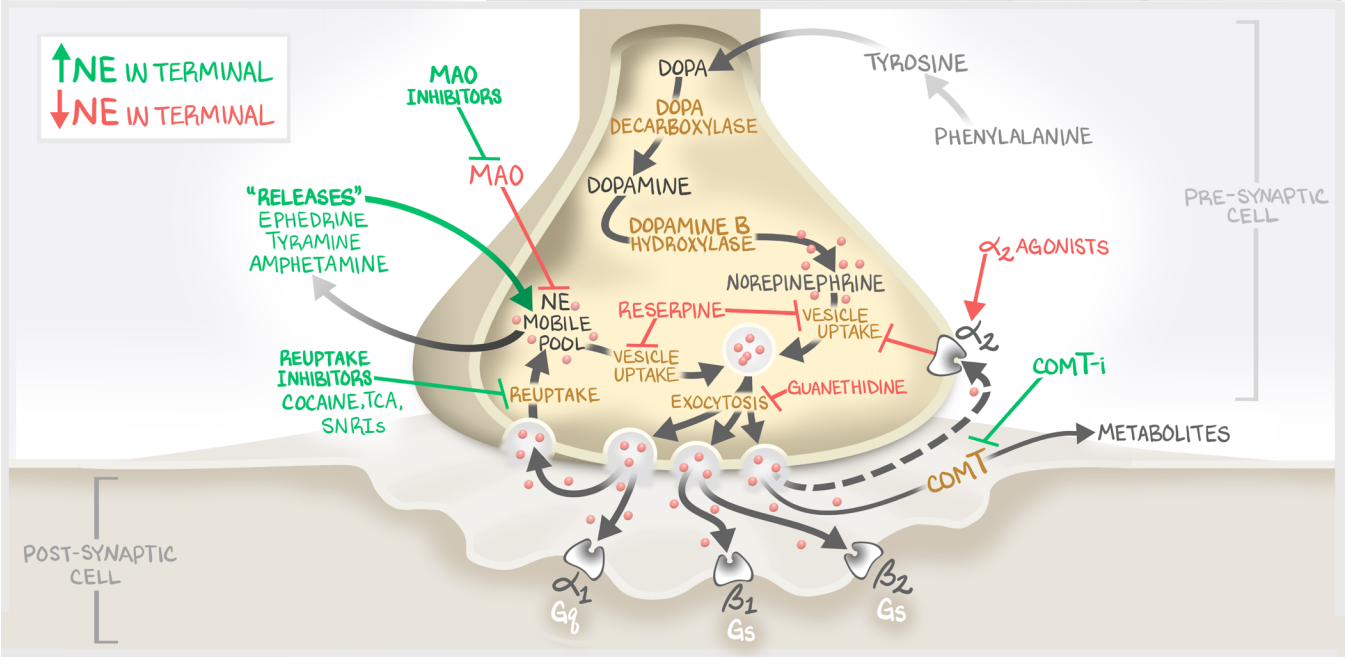


Figure 10.3: Neurotransmitter Cycle for Norepinephrine
The metabolic steps including the enzymes that synthesize norepinephrine de novo are present, but deemphasized. The main emphasis is on norepinephrine reuptake as intact neurotransmitter (majority) with only a mild amount of norepinephrine being metabolized to metabolites. Vesicles filled with norepinephrine fuse with the plasma membrane, norepi activates adrenergic receptors, is then reuptaken intact, entered into the mobile pool, and eventually repackaged into vesicles for the next release. We want you learning that norepinephrine DOES NOT stimulate β_2 receptors, though they are included in this image (1) because norepinephrine does stimulate some β_2s, and (2) this serves as the summary image of Adrenergic Physiology and Pharmacology.

Norepinephrine synthesis is sometimes tested in biochemistry. The main point to commit to memory is that norepinephrine comes from **phenylalanine**, and phenylalanine is an **essential amino acid**—we can't make it, we have to eat it. The rest is low-yield. Phenylalanine is converted through tyrosine into DOPA, DOPA into dopamine, and finally dopamine into norepinephrine. The steps and the enzymes are drawn into Figure 10.3. The reason none of that pathway in the last sentence is bolded and why so little time is spent on it is because none of those steps is involved in the cycle of neurotransmitter release, reuptake, or metabolism. No medication class has an effect on the norepinephrine synthesis pathway.

Norepinephrine neurotransmitter cycle is more high-yield, as there are numerous medication classes that target the cycle. The most important thing is to NOT learn norepinephrine as a variant of the acetylcholine cycle. There are so many superficial similarities that it is tempting to map norepinephrine over acetylcholine. Don't do that. Learn norepinephrine release and metabolism as a completely separate entity.

Norepi (NE) is **packaged into a vesicle** and brought to the axon terminus on microtubules, and there the preformed vesicle is parked. With presynaptic depolarization, there's **vesicle fusion** and **neurotransmitter release** through exocytosis. Norepi enters the synaptic space. It then "does stuff" (activates various adrenergic receptors depending on the tissue innervated). **Intact neurotransmitter** is then recycled back into the presynaptic terminal. This **reuptake** of norepi is one way the norepi signal is terminated (postsynaptic receptors are activated only when norepi is present). The intact neurotransmitter enters the **mobile norepi pool**—intact neurotransmitter not yet packaged back into the vesicle. The cycle then continues where this paragraph began—norepi packaged into vesicles.

Three mechanisms **regulate** norepi synaptic activity. The first is **reuptake** of intact norepi. The second is **active metabolism** (degradation to metabolites) in the synaptic cleft by **COMT**. And thirdly, there's **norepi activation** of **presynaptic α_2 channels** that are **inhibitory** to norepi release. The idea is that the nerve will keep reusing whatever it has (recycling it through reuptake); the COMT will break down a little, but the neuron can always make more, so the real regulatory step is to **self-limit norepi release** with a feedback mechanism **by norepi that inhibits norepi** (presynaptic α_2).

Evaluating Figure 10.3 shows that all of the medications that are involved in norepinephrine metabolism at the synatptic cleft are **indirect agonists**, except for α_2 agonists.

Antagonizing reuptake (reuptake inhibitors) or degradation (MAOI, COMT) increases the norepi effect. **Antagonizing** packaging into vesicles (reserpine) or exocytosis (guanethidine) decreases the norepi effect. **Agonists** for α_2 (clonidine) decrease the norepi effect.

Of special note, the boards love to test **monoamine oxidase inhibitors** (MAOI), used to treat depression by increasing norepinephrine in the brain, and **tyramine**, a substance found in wine and cheese. Tyramine is ingested, and acts as a "releaser," forcing norepinephrine out of the mobile pool and back into the synaptic cleft. MAOIs inhibit the inhibitor, thereby disinhibiting norepinephrine release. The intended effect of MAOIs is the central nervous system's having more norepi and therefore less depression. The side effect is that MAOIs and tyramine can work synergistically on the peripheral neurons and cause **malignant hypertension**.

Drugs like MAOIs, reserpine, and tyramine come up on exams. But because of their toxicities and since the advent of more specific, targeted therapies, these drugs are rarely used in practice.